	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error Definition	Errors
1	BRS	L1	10909	epidermal adj growth adj factor	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/07/01 12:21			0
2	BRS	L2	1281	(epidermal adj growth adj factor) same (modif$7 or substitut$3)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/07/01 12:22			0
3	BRS	L3	961	(epidermal adj growth adj factor) same (analog$2 or derivative$1)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/07/01 12:23			0
4	BRS	L4	473	(tyrosine adj analog) or (Arginine adj analog)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/07/01 12:24			0
5	BRS	L5	0	(2 or 3) same 4	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/07/01 12:26			0
6	BRS	L6	0	(tic or citrulline) same (2 or 3)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/07/01 12:25			0
7	BRS	L7	342	laminin adj receptor	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/07/01 12:26			0
8	BRS	L8	13	7 same (agonist or antagonist)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/07/01 12:26			0
9	BRS	L9	1	(2 or 3) same 8	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/07/01 12:27			0
10	BRS	L10	1	(2 or 3) same 7	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/07/01 12:27			0
11	BRS	L11	2408	(endothelial adj cell) same wound$3	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/07/01 12:29			0

	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error Definition	Errors
12	BRS	L12	992	retinopathy same prematurity	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/07/01 12:29			0
13	BRS	L14	1	(11 or 12) same (2 or 3) same 7	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/07/01 12:30			0
14	BRS	L13	5	(11 or 12) same (2 or 3)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/07/01 12:30			0

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FILE 'MEDLINE' ENTERED AT 12:37:08 ON 01 JUL 2003

FILE 'CAPLUS' ENTERED AT 12:37:08 ON 01 JUL 2003
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COPYRIGHT (C) 2003 BIOLOGICAL ABSTRACTS INC.(R)

FILE 'EMBASE' ENTERED AT 12:37:08 ON 01 JUL 2003
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FILE 'SCISEARCH' ENTERED AT 12:37:08 ON 01 JUL 2003
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FILE 'AGRICOLA' ENTERED AT 12:37:08 ON 01 JUL 2003

=> s epidermal growth factor
L1      140324 EPIDERMAL GROWTH FACTOR

=> s l1 (p)(analog or derivati? or modif? or substitut?)
L2        9279 L1 (P)(ANALOG OR DERIVATI? OR MODIF? OR SUBSTITUT?)

=> s l2 (p) (tyrosine anlog)
L3           0 L2 (P) (TYROSINE ANLOG)

=> s l2 (p)(arginine anlog)
L4           0 L2 (P)(ARGININE ANLOG)

=> s tyrosine anlog
L5           0 TYROSINE ANLOG

=> s arginine analog
L6        1596 ARGININE ANALOG

=> s tyrosine analog
L7         432 TYROSINE ANALOG

=> s (l6 or l7) (p) l1
L8           7 (L6 OR L7) (P) L1

=> duplicate remove l8
DUPLICATE PREFERENCE IS 'CAPLUS, BIOSIS'
KEEP DUPLICATES FROM MORE THAN ONE FILE?  Y/(N):n
PROCESSING COMPLETED FOR L8
L9           7 DUPLICATE REMOVE L8 (0 DUPLICATES REMOVED)

=> d l9 1-7 ibib abs

L9   ANSWER 1 OF 7  CAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:        2003:449475  CAPLUS
TITLE:                   The activation mechanism of the epidermal growth
                         factor receptor
AUTHOR(S):               Saito, Kazuki; Ogiso, Hideo; Ishitani, Ryuichiro;
                         Nureki, Osamu; Fukai, Shuya; Yamanaka, Mari; Kim,
                         Jae-Hoon; Shirouzu, Mikako; Yokoyama, Shigeyuki
CORPORATE SOURCE:        Yokoyama CytoLogic Project, ERATO, Japan Science and
                         Technology Corporation, Yokohama, 230-0045, Japan
SOURCE:                  Peptide Science (2003), Volume Date 2002, 39th, 93-96
                         CODEN: PSCIFQ; ISSN: 1344-7661
PUBLISHER:               Japanese Peptide Society
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   Cellular signaling to and from the   ***epidermal***     ***growth***
       ***factor***   (EGF) receptor has been studied.  First, the crystal
     structure of the complex between EGF and the receptor ectodomains was
     elucidated.  The structure provides a mol. basis for the dimerization
     mechanism of the ligand-activated receptor.  Next, a speck regulatory
     system that switches the downstream pathway of the receptor on and off has
     been developed, by the use of an unnatural phospho-  ***tyrosine***
       ***analog***   for the autophosphorylation site of the receptor.  In
     combination with a mutant of the Grb2-SH2 domain, which accepts the
     unnatural amino acid, it would provide a novel tool for analyzing the
     signaling from the EGF receptor in the intracellular network.
```

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:294219 CAPLUS
Correction of: 2001:168136
DOCUMENT NUMBER: 134:337614
Correction of: 134:233606
TITLE: Nucleic acid-based ribozyme and DNAzyme modulators of gene expression
INVENTOR(S): McSwiggen, James; Usman, Nassim; Blatt, Lawrence; Beigelman, Leonid; Burgin, Alex; Karpeisky, Alexander; Matulic-adamic, Jasenka; Sweedler, David; Draper, Kenneth; Chowrira, Bharat; Stinchcomb, Dan; Beaudry, Amber; Zinnen, Shawn; Lugwig, Janos; Sproat, Brian S.
PATENT ASSIGNEE(S): Ribozyme Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 717 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001016312 A2		20010308	WO 2000-US23998	20000830

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ
RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG

PRIORITY APPLN. INFO.:
US 1999-PV151713 19990831
US 1999-406643 19990927
US 1999-PV156467 19990927
US 1999-PV156236 19990927
US 1999-436430 19991108
US 1999-PV169100 19991206
US 1999-PV173612 19991229
US 1999-474432 19991229
US 1999-476387 19991230
US 2000-498824 20000204
US 2000-531025 20000320
US 2000-PV197769 20000414
US 2000-578223 20000523

AB Novel nucleic acid mols. useful as inhibitors of gene expression, compns., and methods for their use are provided. The invention features novel nucleic acid-based techniques (e.g., enzymic nucleic acid mols. (ribozymes), antisense nucleic acids, 2-5A antisense chimeras, triplex DNA, and antisense nucleic acids contg. RNA-cleaving chem. groups) and their use to modulate the expression of mol. targets impacting the development and progression of cancers, diabetes, obesity, Alzheimer's disease diseases, age-related diseases, and/or hepatitis B infections and related conditions. Catalytic nucleic acids were designed for site-specific cleavage of human mRNA targets encoding protein tyrosine phosphatase 1b, methionine aminopeptidase, .beta.-secretase, presenilin-1, epidermal growth factor receptor-2 (HER2/c-erb2/neu), phospholamban, telomerase, and hepatitis B virus genes. Methods for chem. synthesis of modified nucleoside triphosphates (NTPs) and RNA polymerase-catalyzed incorporation of modified NTPs into catalytic oligonucleotides are also provided. [This abstr. record os one of 6 records for this document necessitated by the large no. of index entries required to fully index the document and publication system constraints.].

L9 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:691122 CAPLUS
DOCUMENT NUMBER: 131:295932
TITLE: Peptide fragments of murine epidermal growth factor as laminin receptor targets for treatment of angiogenic diseases
INVENTOR(S): Nelson, John; Walker, Brian; McFerran, Neil; Harriott, Patrick
PATENT ASSIGNEE(S): The Queen's University of Belfast, UK
SOURCE: PCT Int. Appl., 35 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9954356	A1	19991028	WO 1999-GB1211	19990421
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9936168	A1	19991108	AU 1999-36168	19990421
EP 1073679	A1	20010207	EP 1999-918126	19990421
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: GB 1998-8407 A 19980422
WO 1999-GB1211 W 19990421

AB The present invention provides the use of natural, synthetic or modified peptide factors derived from murine ***epidermal*** ***growth*** ***factor*** in the treatment of angiogenic diseases by targeting laminin receptors. The invention provides agonists and antagonists which may be modified to prevent proteolytic degrdn. Use of the invention to treat retinopathy of prematurity and promote wound healing is envisaged. The peptide factors of the invention are based on amino acid residues 33 to 42 of murine ***epidermal*** ***growth*** ***factor*** (mEGF). The amino acid sequence of mEGF-(33-42) is CVIGYSGDRC. Preferred substitutions include the use of ***tyrosine*** ***analogs*** at position 5 and ***arginine*** ***analogs*** at position 9. Preferably the peptide factor is capped at the N terminal with an acetyl group and at the C terminal with an amide group. Preferably the thiol groups of cysteines are capped with acetamido Me groups. The advantages of the invention, and the ways in which disadvantages of previously known arrangements are overcome include: (1) Unlike the native laminin receptor ligand (laminin.beta.-1925_933), which is angiogenic in human models, the mEGF33_42-derived agents are anti-angiogenic in human models, (2) mEGF33_42 has the advantage of inhibiting both laminin- and EGF-stimulated angiogenesis, and (3) mEGF33_42 prevents tumor cell attachment to basement membranes.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:532694 CAPLUS
DOCUMENT NUMBER: 125:211528
TITLE: Epidermal growth factor receptor tyrosine kinase inhibitors as potential cancer chemopreventives
AUTHOR(S): Kelloff, Gary J.; Fay, Judith R.; Steele, Vernon E.; Lubet, Ronald A.; Boone, Charles W.; Crowell, James A.; Sigman, Caroline C.
CORPORATE SOURCE: Division Cancer Prevention and Control, National Cancer Institute, Bethesda, MD, 20892, USA
SOURCE: Cancer Epidemiology, Biomarkers & Prevention (1996), 5(8), 657-666
CODEN: CEBPE4; ISSN: 1055-9965
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 108 refs. is presented on the use of ***epidermal*** ***growth*** ***factor*** receptor tyrosine kinase inhibitors as potential cancer chemopreventives. Among the most important targets for chemopreventive intervention and drug development are deregulated signal transduction pathways, and protein tyrosine kinases are key components of these pathways. Loss of tyrosine kinase regulatory mechanisms has been implicated in neoplastic growth; indeed, many oncogenes code for either receptor or cellular tyrosine kinases. Because of its deregulation in many cancers (bladder, breast, cervix, colon, esophagus, head and neck, lung, and prostate), the ***epidermal*** ***growth*** ***factor*** receptor (EGFR) has been selected as a potential target for chemoprevention. Because growth factor networks are redundant, selective inhibition of signaling pathways activated in precancerous and cancerous cells should be possible. Requirements for specific EGFR inhibitors include specificity for EGFR, high potency, activity in intact cells, and activity in vivo. Inhibition of autophosphorylation is preferred, because it should result in total blockade of the signaling pathway. Inhibitors

that compete with substrate rather than at the ATP-binding site are also preferable, because they are [redacted] as likely to inhibit other AT[redacted]using cellular enzymes. Several classes of specific EGFR inhibitors have been synthesized recently, including structures such as benzylidene malononitriles, dianilinophthalimides, quinazolines, pyrimidines, [(alkylamino)methyl]-acrylophenones, enollactones, dihydroxybenzyl-aminosalicylates, 2-thioindoles, aminoflavones, and ***tyrosine*** ***analog*** -contg. peptides. A possible testing strategy for the development of these and other EGFR inhibitors as chemopreventive agents includes the following steps: (a) det. EGFR tyrosine kinase inhibitory activity in vitro; (b) evaluate EGFR specificity and selectivity (relative to other tyrosine kinases and other protein kinases); (c) det. inhibition of EGFR-mediated effects in intact cells; (d) det. inhibition of EGFR-mediated effects in vivo (e.g., in nude mouse tumor xenografts); and (e) det. chemopreventive efficacy in vivo (e.g., in the hamster buccal pouch or mouse or rat bladder).

L9 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:263511 CAPLUS
DOCUMENT NUMBER: 124:285125
TITLE: Induction and activity of nitric oxide synthase in cultured human intestinal epithelial monolayers
AUTHOR(S): Salzman, Andrew L.; Denenberg, Alvin G.; Ueta, Ikuya; O'Connor, Michael; Linn, Stephen C.; Szabo, Csaba
CORPORATE SOURCE: Division Critical Care, Children's Hospital Medical Center, Cincinnati, OH, 45229, USA
SOURCE: American Journal of Physiology (1996), 270(4, Pt. 1), G565-G573
CODEN: AJPHAP; ISSN: 0002-9513
PUBLISHER: American Physiological Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The induction and activity of inducible nitric oxide synthase (iNOS) was examd. in monolayers of DLD-1 cells, an epithelial cell line derived from a human intestinal adenocarcinoma. Induction of iNOS transcription by a combination of the cytokines interferon-.gamma. and IL-1.beta. was inhibited by genistein, pyrrolidine dithiocarbamate, or dexamethasone and unaffected by pretreatment with EGTA, basic fibroblast growth factor (bFGF), ***epidermal*** ***growth*** ***factor*** (EGF), or the isoflavone, daidzein. NO synthesis and iNOS activity were inhibited by nitro-L-arginine Me ester, NG-monomethyl-L-arginine, S-methylisothiourea sulfate, or aminoethylisothiourea, but not by dexamethasone. NO synthesis was potently inhibited by N-.alpha.-p-tosyllysine chloromethyl ketone and hypoxia. In the absence of cytokines, no iNOS induction was obsd. with oxidant stress (H2O2), growth factors (bFGF, EGF), hypoxia, or hypoxia reoxygenation. It was concluded that in this model of the human intestinal epithelium (1) cytokine-mediated induction of iNOS is Ca2+-independent, weakly steroid-sensitive, and may involve the activation of nuclear factor-.kappa.B and a protein tyrosine kinase, and (2) iNOS activity is Ca2+-independent and inhibited by hypoxia, NG-substituted-L- ***arginine*** ***analogs*** , and isothioureas.

L9 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:628695 CAPLUS
DOCUMENT NUMBER: 123:286623
TITLE: Potential mechanism-based tyrosine kinase inhibitors. Part 2. Design and synthesis of peptides containing heterocyclic tyrosine analogs
AUTHOR(S): Andrews, David M.; Gregoriou, Mary; Page, Timothy C. M.; Peach, Josephine M.; Pratt, Andrew J.
CORPORATE SOURCE: Dyson Perrins Lab., Oxford, OX1 3QY, UK
SOURCE: Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (1995), (11), 1335-40
CODEN: JCPRB4; ISSN: 0300-922X
PUBLISHER: Royal Society of Chemistry
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The Fmoc derivs. of two homochiral ***tyrosine*** ***analogs*** , a pyridine N-oxide and a pyridone have been prepd. in high stereochem. purity. Solid-phase synthesis has been used to prep. a decapeptide substrate for the tyrosine kinase domain of ***epidermal*** ***growth*** ***factor*** . Two decapeptides, which incorporate the ***tyrosine*** ***analogs*** in place of tyrosine, and thereby have the potential to act as mechanism-based inhibitors of ***epidermal*** ***growth*** ***factor*** tyrosine kinase, have been synthesized and

found to inhibit the aforementioned kinase.

L9 ANSWER 7 OF 7 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1992:111086 BIOSIS
DOCUMENT NUMBER: BR42:51086
TITLE: INHIBITION OF EGF-STIMULATED PHOSPHOLIPASE A2 ACTIVITY BY THE TYRPHOSTIN AG213 IN LESION-FREE PSORIATIC EPIDERMIS.
AUTHOR(S): ILDERTON E; WILKINSON S; YARDLEY H J
CORPORATE SOURCE: DEP. DERMATOL., NORTH STAFFORDSHIRE HOSP. CENTRE, STOKE-ON-TRENT.
SOURCE: ANNUAL MEETING OF THE BRITISH SOCIETY FOR INVESTIGATIVE DERMATOLOGY, LEICESTER, ENGLAND, UK, SEPTEMBER 26-27, 1991. BR J DERMATOL, (1991) 125 (5), 479. CODEN: BJDEAZ. ISSN: 0007-0963.
DOCUMENT TYPE: Conference
FILE SEGMENT: BR; OLD
LANGUAGE: English

=> d his

(FILE 'HOME' ENTERED AT 12:36:43 ON 01 JUL 2003)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT 12:37:08 ON 01 JUL 2003
L1 140324 S EPIDERMAL GROWTH FACTOR
L2 9279 S L1 (P)(ANALOG OR DERIVATI? OR MODIF? OR SUBSTITUT?)
L3 0 S L2 (P) (TYROSINE ANLOG)
L4 0 S L2 (P)(ARGININE ANLOG)
L5 0 S TYROSINE ANLOG
L6 1596 S ARGININE ANALOG
L7 432 S TYROSINE ANALOG
L8 7 S (L6 OR L7) (P) L1
L9 7 DUPLICATE REMOVE L8 (0 DUPLICATES REMOVED)

=> s laminin receptor
L10 4159 LAMININ RECEPTOR

=> s l10 (p) (agonist or antagonist)
L11 83 L10 (P) (AGONIST OR ANTAGONIST)

=> s l2 (p) L11
L12 1 L2 (P) L11

=> d l12 1 ibib abs

L12 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:691122 CAPLUS
DOCUMENT NUMBER: 131:295932
TITLE: Peptide fragments of murine epidermal growth factor as laminin receptor targets for treatment of angiogenic diseases
INVENTOR(S): Nelson, John; Walker, Brian; McFerran, Neil; Harriott, Patrick
PATENT ASSIGNEE(S): The Queen's University of Belfast, UK
SOURCE: PCT Int. Appl., 35 pp. CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9954356	A1	19991028	WO 1999-GB1211	19990421
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9936168	A1	19991108	AU 1999-36168	19990421
EP 1073679	A1	20010207	EP 1999-918126	19990421
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,				

IE, FI
PRIORITY APPLN. INFO.: GB 1998-8407 A 19980[redacted]
WO 1999-GB1211 W 19990[redacted]

AB The present invention provides the use of natural, synthetic or ***modified*** peptide factors derived from murine ***epidermal*** ***growth*** ***factor*** in the treatment of angiogenic diseases by targeting ***laminin*** ***receptors*** . The invention provides ***agonists*** and ***antagonists*** which may be ***modified*** to prevent proteolytic degrdn. Use of the invention to treat retinopathy of prematurity and promote wound healing is envisaged. The peptide factors of the invention are based on amino acid residues 33 to 42 of murine ***epidermal*** ***growth*** ***factor*** (mEGF). The amino acid sequence of mEGF-(33-42) is CVIGYSGDRC. Preferred ***substitutions*** include the use of tyrosine ***analogs*** at position 5 and arginine ***analogs*** at position 9. Preferably the peptide factor is capped at the N terminal with an acetyl group and at the C terminal with an amide group. Preferably the thiol groups of cysteines are capped with acetamido Me groups. The advantages of the invention, and the ways in which disadvantages of previously known arrangements are overcome include: (1) Unlike the native ***laminin*** ***receptor*** ligand (laminin.beta.-1925_933), which is angiogenic in human models, the mEGF33_42-derived agents are anti-angiogenic in human models, (2) mEGF33_42 has the advantage of inhibiting both laminin- and EGF-stimulated angiogenesis, and (3) mEGF33_42 prevents tumor cell attachment to basement membranes.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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     (FILE 'HOME' ENTERED AT 12:36:43 ON 01 JUL 2003)

     FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT
     12:37:08 ON 01 JUL 2003
L1       140324 S EPIDERMAL GROWTH FACTOR
L2         9279 S L1 (P)(ANALOG OR DERIVATI? OR MODIF? OR SUBSTITUT?)
L3            0 S L2 (P) (TYROSINE ANLOG)
L4            0 S L2 (P)(ARGININE ANLOG)
L5            0 S TYROSINE ANLOG
L6         1596 S ARGININE ANALOG
L7          432 S TYROSINE ANALOG
L8            7 S (L6 OR L7) (P) L1
L9            7 DUPLICATE REMOVE L8 (0 DUPLICATES REMOVED)
L10        4159 S LAMININ RECEPTOR
L11          83 S L10 (P) (AGONIST OR ANTAGONIST)
L12           1 S L2 (P) L11

=> s l2 (p0 l10
MISSING OPERATOR 'L14 (P0'
The search profile that was entered contains terms or
nested terms that are not separated by a logical operator.

=> s l2 (p) l10
L13           3 L2 (P) L10

=> duplicate remove l13
DUPLICATE PREFERENCE IS 'MEDLINE, CAPLUS, BIOSIS'
KEEP DUPLICATES FROM MORE THAN ONE FILE?  Y/(N):n
PROCESSING COMPLETED FOR L13
L14           2 DUPLICATE REMOVE L13 (1 DUPLICATE REMOVED)

=> s l14 not l12
L15           1 L14 NOT L12

=> d l15 1 ibib abs

L15  ANSWER 1 OF 1     MEDLINE
ACCESSION NUMBER:   86199471     MEDLINE
DOCUMENT NUMBER:    86199471   PubMed ID: 3457945
TITLE:              Chemotaxis of human gingival epithelial cells to laminin. A
                    mechanism for epithelial cell apical migration.
AUTHOR:             Terranova V P; Lyall R M
SOURCE:             JOURNAL OF PERIODONTOLOGY, (1986 May) 57 (5) 311-7.
                    Journal code: 8000345. ISSN: 0022-3492.
PUB. COUNTRY:       United States
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
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LANGUAGE: English
FILE SEGMENT: Dental Journa Priority Journals
ENTRY MONTH: 198606
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19900321
Entered Medline: 19860613

AB Laminin, a large glycoprotein (Mr = 10(6)) and a major component of basement membrane, is shown here to be a potent chemoattractant for human gingival epithelial cells. Laminin stimulated chemotaxis and chemokinesis of gingival epithelial cells in the ***modified*** Boyden chamber assay. This effect appeared to be ***laminin*** ***receptor*** mediated. Gingival epithelial cells were shown to bind laminin (Kd = 2.0 nM) with 10,000 to 30,000 binding sites per cell. Antilaminin antibody, which inhibited laminin binding, inhibited the chemotactic response of epithelial cells to laminin, while antifibronectin was without effect. Fibronectin was not as potent a chemoattractant as laminin. Other biological response ***modifiers*** were also tested; of these, Type IV collagen and ***epidermal*** ***growth*** ***factor*** were active as chemoattractants, although not as effective in inducing chemotaxis as laminin. The data indicate that laminin and other components of basement membrane may be important in regulating the migration and growth of gingival epithelial cells.

=> d his

(FILE 'HOME' ENTERED AT 12:36:43 ON 01 JUL 2003)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT 12:37:08 ON 01 JUL 2003

L1 140324 S EPIDERMAL GROWTH FACTOR
L2 9279 S L1 (P)(ANALOG OR DERIVATI? OR MODIF? OR SUBSTITUT?)
L3 0 S L2 (P) (TYROSINE ANLOG)
L4 0 S L2 (P)(ARGININE ANLOG)
L5 0 S TYROSINE ANLOG
L6 1596 S ARGININE ANALOG
L7 432 S TYROSINE ANALOG
L8 7 S (L6 OR L7) (P) L1
L9 7 DUPLICATE REMOVE L8 (0 DUPLICATES REMOVED)
L10 4159 S LAMININ RECEPTOR
L11 83 S L10 (P) (AGONIST OR ANTAGONIST)
L12 1 S L2 (P) L11
L13 3 S L2 (P) L10
L14 2 DUPLICATE REMOVE L13 (1 DUPLICATE REMOVED)
L15 1 S L14 NOT L12

=> s (endothelial cell) (p) wound?
4 FILES SEARCHED...
L16 5338 (ENDOTHELIAL CELL) (P) WOUND?

=> s retinopathy (p) prematurity
L17 7738 RETINOPATHY (P) PREMATURITY

=> s (l16 or l17) (p) (12 or 14)
L18 1629 (L16 OR L17) (P) (12 OR 14)

=> s (l16 or l17) (p) (l12 or l14)
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L109) (P) '
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L110) (P) '
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L111) (P) '
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L112) (P) '
L19 1 (L16 OR L17) (P) (L12 OR L14)

=> s l19 not l12
L20 0 L19 NOT L12

=> d his

(FILE 'HOME' ENTERED AT 12:36:43 ON 01 JUL 2003)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT 12:37:08 ON 01 JUL 2003
L1 140324 S EPIDERMAL GROWTH FACTOR

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L2          9279 S L1 (P)(ANALOG OR DERIVATI? OR MODIF? OR SUBSTITUT?)
L3             0 S L2 (P) (TYROSIN[redacted]LOG)
L4             0 S L2 (P)(ARGININE [redacted]LOG)
L5             0 S TYROSINE ANLOG
L6          1596 S ARGININE ANALOG
L7           432 S TYROSINE ANALOG
L8             7 S (L6 OR L7) (P) L1
L9             7 DUPLICATE REMOVE L8 (0 DUPLICATES REMOVED)
L10         4159 S LAMININ RECEPTOR
L11           83 S L10 (P) (AGONIST OR ANTAGONIST)
L12            1 S L2 (P) L11
L13            3 S L2 (P) L10
L14            2 DUPLICATE REMOVE L13 (1 DUPLICATE REMOVED)
L15            1 S L14 NOT L12
L16         5338 S (ENDOTHELIAL CELL) (P) WOUND?
L17         7738 S RETINOPATHY (P) PREMATURITY
L18         1629 S (L16 OR L17) (P) (12 OR 14)
L19            1 S (L16 OR L17) (P) (L12 OR L14)
L20            0 S L19 NOT L12

=> log y
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                      ENTRY    SESSION
FULL ESTIMATED COST                                   82.18      82.39

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                      ENTRY    SESSION
CA SUBSCRIBER PRICE                                   -4.56      -4.56

STN INTERNATIONAL LOGOFF AT 12:48:14 ON 01 JUL 2003
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Kam 09/673,785

=> d his 1

(FILE 'MEDLINE, HCAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT 15:22:07 ON 01 JUL 2003)
L29 35 DUP REM L28 (44 DUPLICATES REMOVED)

=> d que l29
L1 1 SEA FILE=REGISTRY CITRULLINE/CN
L5 18609 SEA NELSON J?/AU
L6 7210 SEA WALKER B?/AU
L7 1 SEA MC FERRAN N?/AU
L8 181 SEA MCFERRAN N?/AU
L9 367 SEA HARRIOTT P?/AU
L10 26078 SEA (L5 OR L6 OR L7 OR L8 OR L9)
L11 2644 SEA MOUSE(5A) EPIDERMAL(3A) GROWTH(3A) FACTOR#
L12 3186 SEA MOUSE(5A) EGF#
L13 904 SEA MURINE(5A) EGF#
L14 655 SEA MURINE(5A) EPIDERMAL(3A) GROWTH(3A) FACTOR#
L15 6166 SEA (L11 OR L12 OR L13 OR L14)
L16 22 SEA L10 AND L15
L17 12 SEA L16 AND LAMININ#
L28 79 SEA (L17 OR L18 OR L19 OR L20 OR L21 OR L22) OR L27
L29 35 DUP REM L28 (44 DUPLICATES REMOVED)

=> d ibib abs l29 1-35

L29 ANSWER 1 OF 35 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2003111936 MEDLINE
DOCUMENT NUMBER: 22499956 PubMed ID: 12612091
TITLE: Brain lipid **binding** protein in axon-Schwann cell interactions and peripheral nerve tumorigenesis.
AUTHOR: Miller Shyra J; Li Hongzhen; Rizvi Tilat A; Huang Yuan; Johansson Gunnar; Bowersock Jason; Sidani Amer; Vitullo John; Vogel Kristine; Parysek Linda M; DeClue Jeffrey E; Ratner Nancy
CORPORATE SOURCE: Department of Cell Biology, Neurobiology and Anatomy, University of Cincinnati College of Medicine, 231 Bethesda Avenue, Cincinnati, OH 45267-0521, USA.
CONTRACT NUMBER: NS 28840 (NINDS)
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2003 Mar) 23 (6) 2213-24. Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200304
ENTRY DATE: Entered STN: 20030311
Last Updated on STN: 20030417
Entered Medline: 20030415
AB Loss of axonal contact characterizes Schwann cells in benign and malignant peripheral nerve sheath tumors (MPNST) from neurofibromatosis type 1 (NF1) patients. Tumor Schwann cells demonstrate NF1 **mutations**, elevated Ras activity, and aberrant epidermal growth factor receptor (EGFR) expression. Using cDNA microarrays, we found that brain lipid **binding** protein (BLBP) is elevated in an **EGFR**-positive subpopulation of Nf1 **mutant mouse** Schwann cells (Nf1(-/-) TXF) that grows away from axons; BLBP expression was not affected by farnesyltransferase inhibitor, an inhibitor of H-Ras. BLBP

Search completed by David Schreiber 308-4292

was also detected in EGFR-positive cell lines derived from Nf1:p53 double **mutant** mice and human MPNST. BLBP expression was induced in normal Schwann cells following transfection with EGFR but not H-Ras12V. Furthermore, EGFR-mediated BLBP expression was not inhibited by dominant-negative H-Ras, indicating that BLBP expression is downstream of Ras-independent EGFR signaling. BLBP-**blocking** antibodies enabled process outgrowth from Nf1(-/-) TXF cells and restored interaction with axons, without affecting cell proliferation or migration. Following injury, BLBP expression was induced in normal sciatic nerves when nonmyelinating Schwann cells remodeled their processes. These data suggest that BLBP, stimulated by Ras-independent pathways, regulates Schwann cell-axon interactions in normal peripheral nerve and peripheral nerve tumors.

L29 ANSWER 2 OF 35 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2003:88665 BIOSIS
DOCUMENT NUMBER: PREV200300088665
TITLE: The blood-CSF barrier in culture: Development of a primary culture and transepithelial transport model from choroidal epithelial cells.
AUTHOR(S): Zheng, Wei (1); Zhao, Qiuqu
CORPORATE SOURCE: (1) Division of Environmental Health Sciences, School of Public Health, Columbia University, New York, NY, USA USA
SOURCE: Wise, Clare [Editor]. Methods in Molecular Biology, (2002) Vol. 188, pp. 99-114. Methods in Molecular Biology. Epithelial cell culture protocols. print.
Publisher: Humana Press Inc. 999 Riverview Drive, Suite 208, Totowa, NJ, 07512, USA.
ISSN: 1064-3745. ISBN: 0-89603-893-9 (cloth).
DOCUMENT TYPE: Book
LANGUAGE: English

L29 ANSWER 3 OF 35 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:605394 BIOSIS
DOCUMENT NUMBER: PREV200200605394
TITLE: Transcriptomic responses underpinning renal tubulointerstitial fibrosis as identified by DNA oligonucleotide microarray technology.
AUTHOR(S): Higgins, Debra F. (1); Lappin, David W. P. (1); Isaka, Yoshi; Watson, Ronald W.; Godson, Catherine (1); Imai, Enyu; Fitzpatrick, John M.; Brady, Hugh R. (1)
CORPORATE SOURCE: (1) Medicine and Therapeutics, Conway Institute, Mater Misericordiae Hospital, University College Dublin, Dublin Ireland
SOURCE: Journal of the American Society of Nephrology, (September, 2002) Vol. 13, No. Program and Abstracts Issue, pp. 560A. http://www.jasn.org/. print.
Meeting Info.: Meeting of the American Society of Nephrology Philadelphia, PA, USA October 30-November 04, 2002 American Society of Nephrology
. ISSN: 1046-6673.
DOCUMENT TYPE: Conference
LANGUAGE: English

L29 ANSWER 4 OF 35 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:742487 HCAPLUS
DOCUMENT NUMBER: 138:36912
TITLE: Caveolin-1 Phosphorylation in Human Squamous and Epidermoid Carcinoma Cells: Dependence on ErbB1

Expression and Src Activation
AUTHOR(S): Kim, Yong-Nyun; Dam, Phuongan; Bertics, Paul J.
CORPORATE SOURCE: Department of Biomolecular Chemistry, University of Wisconsin, Madison, WI, 53706-1532, USA
SOURCE: Experimental Cell Research (2002), 280(1), 134-147
CODEN: ECREAL; ISSN: 0014-4827
PUBLISHER: Elsevier Science
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Previous studies have shown that EGF can induce the tyrosine phosphorylation of caveolin-1 in **murine** fibroblasts following ErbB1 (**EGF** receptor) **mutation** or overexpression, but the cell signaling events linking EGF action with caveolin phosphorylation are not fully established. In this regard, we examd. multiple human carcinoma cell lines that express various ErbB family members, including A431 epidermoid carcinoma cells and several squamous carcinoma cell lines. In all cases, EGF treatment induced the tyrosine phosphorylation of caveolin-1 in a time- and EGF dose-dependent manner, and immunoblotting anal. revealed that this phosphorylation occurred at tyrosine-14. The EGF-dependent phosphorylation of caveolin-1 was obsd. at low temps. (4.degree.) and was enhanced by caveolae-disrupting agents (cyclodextrin), suggesting that this EGF-dependent system is in a low temp.-stable arrangement that allows for their interaction under conditions where mobility in the membrane is altered. To further assess the events linking EGF action with caveolin phosphorylation, we evaluated the ligand specificity of these responses and their dependence on known effectors of EGF receptor function. We obsd. that EGF and HB-EGF, but not heregulin, promoted caveolin-1 phosphorylation in A431 cells, suggesting that these responses are linked to EGF receptor activation and not solely occurring via the activation of other endogenous ErbB family members. In addn., the EGF-induced phosphorylation of caveolin-1 in A431 cells was **blocked** by the Src kinase antagonists PP1 and PP2, but not by the MEK inhibitor PD98059, the phosphoinositide 3-kinase inhibitors LY294002 and wortmannin, or cytoskeleton-disrupting agents, such as cytochalasin D, colchicine, and nocadazole. Altogether, these data indicate that multiple human carcinoma cells exhibit an EGF receptor-dependent tyrosine phosphorylation of caveolin-1 and that this process is sensitive to Src family kinase inhibitors. These observations support a role for caveolin tyrosine phosphorylation in the profile of cellular responses by which Src potentiates cancer progression following EGF receptor overexpression.

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 5 OF 35 MEDLINE
ACCESSION NUMBER: 2002000487 MEDLINE
DOCUMENT NUMBER: 21601628 PubMed ID: 11581249
TITLE: Phosphatidylinositol-4-phosphate 5-kinase-1beta is essential for epidermal growth factor receptor-mediated endocytosis.
AUTHOR: Barbieri M A; Heath C M; Peters E M; Wells A; Davis J N; Stahl P D
CORPORATE SOURCE: Department of Cell Biology and Physiology, Washington University School of Medicine, 660 S. Euclid Ave., St. Louis, MO 63110-7463, USA.
CONTRACT NUMBER: AI 20015 (NIAID)
AI 35884 (NIAID)
GM 42259 (NIGMS)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 Dec 14) 276 (50) 47212-6.

Search completed by David Schreiber 308-4292

Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20020102
Last Updated on STN: 20030105
Entered Medline: 20020124

AB Phosphatidylinositol-4,5-bisphosphate (PIP(2)) is known to play an important role in signal transduction and membrane trafficking. We show that one enzyme responsible for PIP(2) production, phosphatidylinositol-4-phosphate 5-kinase type 1beta (PIPKbeta), is essential for epidermal growth factor receptor (EGFR)-mediated endocytosis. Expression of **murine** PIPKbeta in NR6 cells expressing **EGFR** strikingly increased receptor internalization. Moreover, the kinase was shown to form an immunoprecipitable complex with EGFR. Expression of either a truncated kinase or a kinase dead **mutant** inhibited EGFR endocytosis and also **blocked** the membrane recruitment of PIPKbeta and both clathrin light chain and dynamin. Our results delineate a novel mechanism by which PIPKbeta regulates receptor-mediated endocytosis and receptor tyrosine kinase membrane traffic.

L29 ANSWER 6 OF 35 MEDLINE DUPLICATE 2

ACCESSION NUMBER: 2001481689 MEDLINE
DOCUMENT NUMBER: 21417306 PubMed ID: 11526457
TITLE: Electrotransfer of naked DNA in the skeletal muscles of animal models of muscular dystrophies.
AUTHOR: Vilquin J T; Kennel P F; Paturneau-Jouas M; Chapdelaine P; Boissel N; Delaere P; Tremblay J P; Scherman D; Fiszman M Y; Schwartz K
CORPORATE SOURCE: INSERM U 523, Hopital de la Salpetriere, Paris, France.
SOURCE: GENE THERAPY, (2001 Jul) 8 (14) 1097-107.
Journal code: 9421525. ISSN: 0969-7128.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 20010830
Last Updated on STN: 20011015
Entered Medline: 20011011

AB The electrotransfer of naked DNA has recently been adapted to the transduction of skeletal muscle fibers. We investigated the short- and long-term efficacy of this methodology in wild-type animals and in mouse models of congenital muscular dystrophy (dy/dy, dy(2J)/dy(2J)), or Duchenne muscular dystrophy (mdx/mdx). Using a reporter construct, the short-term efficacy of fiber transduction reached 40% and was similar in wild-type, dy/dy and dy(2J)/dy(2J) animals, indicating that ongoing muscle fibrosis was not a major obstacle to the electrotransfer-mediated gene transfer. Although the complete rejection of transduced fibers was observed within 3 weeks in the absence of immunosuppression, the persistency was prolonged over 10 weeks when transient or continuous immunosuppressive regimens were used. Using therapeutic plasmids, we demonstrated that electrotransfer also allowed the transduction of large constructs encoding the **laminin** alpha2 chain in dy/dy **mouse**, or a chimeric dystrophin-**EGFP** protein in mdx/mdx **mouse**. The correct sarcolemmal localization of these structural proteins demonstrated the functional relevance of their expression in

vivo, with a diffusion domain estimated to be 300 to 500 microm. However, degeneration-regeneration events hampered the long-term stability of transduced fibers. Given its efficacy for naked DNA transfer in these models of muscular dystrophies, and despite some limitations, gene electrotransfer methodology should be further explored as a potential avenue for treatment of muscular dystrophies.

L29 ANSWER 7 OF 35 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:779622 HCAPLUS
DOCUMENT NUMBER: 134:1006
TITLE: Epidermal growth factor and membrane trafficking: EGF receptor activation of endocytosis requires Rab5a
AUTHOR(S): Barbieri, M. Alejandro; Roberts, Richard L.; Gumusboga, Aysel; Highfield, Hilary; Alvarez-Dominguez, Carmen; Wells, Alan; Stahl, Philip D.
CORPORATE SOURCE: Department of Cell Biology and Physiology, Washington University School of Medicine, St. Louis, MO, 63110, USA
SOURCE: Journal of Cell Biology (2000), 151(3), 539-550
CODEN: JCLBA3; ISSN: 0021-9525
PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Activated epidermal growth factor receptors recruit various intracellular proteins leading to signal generation and endocytic trafficking. Although activated receptors are rapidly internalized into the endocytic compartment and subsequently degraded in lysosomes, the linkage between signaling and endocytosis is not well understood. Here EGF stimulation of NR6 cells induces a specific, rapid and transient activation of Rab5a. EGF also enhanced translocation of the Rab5 effector, early endosomal autoantigen 1 (EEA1), from cytosol to membrane. The activation of endocytosis, fluid phase and receptor mediated, by EGF was enhanced by Rab5a expression, but not by Rab5b, Rab5c, or Rab5a truncated at the NH2 and/or C-terminus. Dominant neg. Rab5a (Rab5:N34) **blocked** EGF-stimulated receptor-mediated and fluid-phase endocytosis. EGF activation of Rab5a function was dependent on tyrosine residues in the C-terminal domain of the EGF receptor (EGFR). Removal of the entire C-terminus by truncation (c'973 and c'991) abrogated ligand-induced Rab5a activation of endocytosis. A "kinase-dead" EGFR failed to stimulate Rab5a function. However, another EGF receptor **mutant** (c'1000), with the kinase domain intact and a single autophosphorylation site effectively signaled Rab5 activation. These results indicate that EGFR and Rab5a are linked via a cascade that results in the activation of Rab5a and that appears essential for internalization. The results point to an interdependent relationship between receptor activation, signal generation and endocytosis.
REFERENCE COUNT: 62 THERE ARE 62 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 8 OF 35 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:154245 BIOSIS
DOCUMENT NUMBER: PREV200000154245
TITLE: Cloning and expression throughout mouse development of mFat1, a homologue of the Drosophila tumour suppressor gene fat.
AUTHOR(S): Cox, Barnaby; Hadjantonakis, Anna-Katerina; Collins, Jane E.; Magee, Anthony I. (1)
CORPORATE SOURCE: (1) Division of Membrane Biology, National Institute for

Medical Research, Ridgeway, Mill Hill, London, NW7 1AA UK
SOURCE: Developmental Dynamics., (March, 2000) Vol. 217, No. 3, pp. 233-240.
ISSN: 1058-8388.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB We present the entire sequence of the mouse Fat orthologue (mFat1), a protein of 4,588 amino acids with 34 cadherin repeats, 27 potential N-glycosylation sites, five EGF repeats and a **laminin** A G-motif in its extracellular domain. A single transmembrane region is followed by a cytoplasmic domain containing putative catenin-binding sequences. mFat1 shows high homology to human FAT and lesser homology to Drosophila Fat. The sequence of this giant cadherin suggests that it is unlikely to have a homophilic adhesive function, but may mediate heterophilic adhesion or play a signalling role. Expression analysis shows that the mfat1 gene is expressed early in pre-implantation mouse development, at the compact eight cell stage. Whole-mount and section in situ analyses show that transcripts are widely expressed throughout post-implantation development, most notably in the limb buds, branchial arches, forming somites, and in particular in the proliferating ventricular zones in the brain, being down-regulated as cells cease dividing. RT-PCR detects widespread expression in the adult suggesting a role in proliferation and differentiation of many tissues and cell types.

L29 ANSWER 9 OF 35 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:691122 HCAPLUS
DOCUMENT NUMBER: 131:295932
TITLE: Peptide fragments of **murine epidermal growth factor** as **laminin** receptor targets for treatment of angiogenic diseases
INVENTOR(S): **Nelson, John; Walker, Brian; McFerran, Neil; Harriott, Patrick**
PATENT ASSIGNEE(S): The Queen's University of Belfast, UK
SOURCE: PCT Int. Appl., 35 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9954356	A1	19991028	WO 1999-GB1211	19990421
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9936168	A1	19991108	AU 1999-36168	19990421
EP 1073679	A1	20010207	EP 1999-918126	19990421
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: GB 1998-8407 A 19980422

Search completed by David Schreiber 308-4292

WO 1999-GB1211 W 19990421

AB The present invention provides the use of natural, synthetic or **modified** peptide **factors** derived from **murine epidermal growth factor** in the treatment of angiogenic diseases by targeting **laminin** receptors. The invention provides agonists and antagonists which may be **modified** to prevent proteolytic degrdn. Use of the invention to treat retinopathy of prematurity and promote wound healing is envisaged. The peptide factors of the invention are based on amino acid residues 33 to 42 of **murine epidermal growth factor** (mEGF). The amino acid sequence of mEGF-(33-42) is CVIGYSGDRC. Preferred **substitutions** include the use of **tyrosine analogs** at position 5 and **arginine analogs** at position 9. Preferably the peptide factor is capped at the N terminal with an acetyl group and at the C terminal with an amide group. Preferably the thiol groups of cysteines are capped with acetamido Me groups. The advantages of the invention, and the ways in which disadvantages of previously known arrangements are overcome include: (1) Unlike the native **laminin** receptor ligand (**laminin** .beta.-1925_933), which is angiogenic in human models, the mEGF33_42-derived agents are anti-angiogenic in human models, (2) mEGF33_42 has the advantage of inhibiting both **laminin**- and EGF-stimulated angiogenesis, and (3) mEGF33_42 prevents tumor cell attachment to basement membranes.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 10 OF 35 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1999:265542 HCAPLUS

DOCUMENT NUMBER: 131:40169

TITLE: Integrin-mediated migration of murine B82L fibroblasts is dependent on the expression of an intact epidermal growth factor receptor

AUTHOR(S): Li, Jing; Lin, Meei-Lih; Wiepz, Gregory J.; Guadarrama, Arturo G.; Bertics, Paul J.

CORPORATE SOURCE: Department of Biomolecular Chemistry, University of Wisconsin, Madison, WI, 53706-1532, USA

SOURCE: Journal of Biological Chemistry (1999), 274(16), 11209-11219
CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB To evaluate the mechanisms by which epidermal growth factor (EGF) regulates actin-based cellular processes such as cell migration, we first examd. the effects of EGF on cell adhesion, which is essential for cell migration. In mouse B82L fibroblasts transfected with the full-length EGF receptor, EGF promotes cell rounding and attenuates cell spreading on fibronectin, **laminin**, and vitronectin, and thus appears to reduce the strength of cell adhesion. Moreover, EGF synergizes with multiple extracellular matrix (ECM) components in the promotion of integrin-mediated cell migration of several different cell types, including fibroblasts and various carcinoma and osteosarcoma cell lines. Interestingly, co-presentation (co-positioning) of EGF with **laminin** or fibronectin is essential for EGF-stimulated migration. When EGF is mixed with the cells instead of the ECM components, it has little effect on cell migration. These results suggest that co-presentation of EGF with ECM components can enhance the polarization

events required for directional cell movement. To identify the EGF receptor elements crit. for the EGF stimulation of cell migration, B82L fibroblasts were transfected with either mutated or wild-type EGF receptors. Surprisingly, we found that B82L-parental cells that lack the EGF receptor are not able to migrate to fibronectin, even though they can adhere to fibronectin. However, the introduction of wild-type EGF receptors into these fibroblasts enables them to migrate toward fibronectin even in the absence of EGF. The requirement of the EGF receptor for cell migration does not appear to result from the secretion of EGF or TGF-.alpha. by the cells transfected with the EGF receptor. Furthermore, cells expressing EGF receptors that are kinase-inactive, or C-terminally truncated, exhibit little migration toward fibronectin, indicating that an intact EGF receptor kinase is required for fibronectin-induced cell migration. In addn., neutralizing anti-EGF receptor antibodies attenuate cell migration in the presence of EGF, and inhibit migration to fibronectin or **laminin** alone. These results further suggest that the EGF receptor is downstream of integrin activation in the signal transduction pathways leading to fibroblast migration.

REFERENCE COUNT: 80 THERE ARE 80 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 11 OF 35 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 1998232202 MEDLINE
DOCUMENT NUMBER: 98232202 PubMed ID: 9572490
TITLE: Epidermal growth factor activation of NF-kappaB is mediated through IkappaBalpha degradation and intracellular free calcium.
AUTHOR: Sun L; Carpenter G
CORPORATE SOURCE: Department of Biochemistry, Vanderbilt University School of Medicine, Nashville, Tennessee 37232-0146, USA.
CONTRACT NUMBER: RO1 CA75195 (NCI)
T32 CA09582 (NCI)
SOURCE: ONCOGENE, (1998 Apr 23) 16 (16) 2095-102.
Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199805
ENTRY DATE: Entered STN: 19980520
Last Updated on STN: 20020919
Entered Medline: 19980514

AB The transcription factor NF-kappa-B is normally sequestered in the cytoplasm by its inhibitory subunit IkappaB. Most extracellular signals activate NF-kappa-B through a mechanism involving the phosphorylation and proteasome-dependent degradation of IkappaB. EGF activates NF-kappaB in A-431 carcinoma cells, which overexpress **EGF** receptors and in **mouse** embryo fibroblasts, which have a normal complement of receptors. Supershift experiments indicate that the NF-kappa-B complexes induced by EGF are composed of p50/p50 homodimers and p65/p50 heterodimers, but not c-rel. EGF stimulation enhances the degradation of IkappaBalpha, but not IkappaBbeta nor an N-terminal deletion **mutant** of IkappaBalpha. Treatment of cells with a proteasome inhibitor, such as ALLN or MG132, **blocks** EGF-mediated NF-kappaB activation, indicating that EGF-induced NF-kappa-B activation requires proteasome-dependent IkappaB degradation. Also, Bapta A/M (a cell-permeable chelator of intracellular calcium) **blocks** EGF-induced NF-kappa-B activation and IkappaBalpha degradation, suggesting

a requirement of intracellular free Ca2+ for this growth factor response. Protein kinase C inhibition, in contrast, did not influence EGF activation of NF-kappaB.

L29 ANSWER 12 OF 35 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 97299067 MEDLINE
DOCUMENT NUMBER: 97299067 PubMed ID: 9154469
TITLE: Humanization of a **mouse** monoclonal antibody that **blocks** the **epidermal growth factor** receptor: recovery of antagonistic activity.
AUTHOR: Mateo C; Moreno E; Amour K; Lombardero J; Harris W; Perez R
CORPORATE SOURCE: Centro de Immunologia Molecular, Habana, Cuba.. cristina@ict.sld.cu
SOURCE: IMMUNOTECHNOLOGY, (1997 Mar) 3 (1) 71-81. Journal code: 9511979. ISSN: 1380-2933.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199707
ENTRY DATE: Entered STN: 19970724
Last Updated on STN: 20000303
Entered Medline: 19970717

AB BACKGROUND: Antibody humanization by transplanting the complementarity determining regions (CDRs) of a murine antibody to a human framework aims to reduce the response of the human immune system against a foreign molecule. Frequently, however, some murine amino acids from the framework have to be retained to recover **binding** affinity. OBJECTIVES: To redesign R3, a mouse monoclonal antibody (mAb) that **binds** the human epidermal growth factor (EGF)-receptor and inhibits the **binding** of EGF, to be a human IgG1. STUDY DESIGN: The light and heavy chains of REI and Eu, respectively, were selected as human immunoglobulin (Ig) frameworks for CDR-grafting based on their high homology with the corresponding sequences of murine R3. Molecular modeling was used to analyze the possible effects of **mutating** murine residues that underlie the CDRs. RESULTS: CDR-grafting dramatically reduced the **binding** capability of the antibody. Molecular modeling suggested that two amino acids (Thr 76 and Thr 93), among five immunoglobulin heavy chain variable region (VH) residues underlying the CDRs, were critical for antigen **binding**. The five residues were **mutated** back to the original murine amino acids in different combinations contained in six variants of humanized antibodies. In agreement with molecular modeling analysis. The variant in which three murine residues were retained (Ser 75, Thr 76 and Thr 93) exhibited a similar capacity to inhibit the **binding** of 125I-labeled EGF to its receptor as compared with the original antibody. This humanized antibody was at least 2-fold less immunogenic in African Green monkeys than the chimeric antibody. CONCLUSIONS: Only very few **mutations** in the frameworks may be necessary to recover the **binding** capability of a humanized antibody. Molecular modeling can serve as a powerful tool to identify residues critical for **binding**.

L29 ANSWER 13 OF 35 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 96421617 MEDLINE
DOCUMENT NUMBER: 96421617 PubMed ID: 8824265
TITLE: **Murine epidermal growth factor** peptide (33-42) binds to a YIGSR-specific **laminin** receptor on both tumor and endothelial

cells.

AUTHOR: **Nelson J**; Scott W N; Allen W E; Wilson D J; **Harriott P**; **McFerran N V**; **Walker B**

CORPORATE SOURCE: Centre for Peptide and Protein Engineering, School of Biology and Biochemistry, The Queen's University of Belfast, Belfast BT9 7BL, Northern Ireland, United Kingdom.

SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 Oct 18) 271 (42) 26179-86.
Journal code: 2985121R. ISSN: 0021-9258.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199611
ENTRY DATE: Entered STN: 19961219
Last Updated on STN: 20000303
Entered Medline: 19961126

AB A **laminin**-antagonist peptide, comprising amino acids 33-42 of **murine epidermal growth factor** (mEGF-(33-42)), interacts with a breast cancer- and endothelial cell-associated receptor, which is specific for the **laminin** B1 chain sequence, CDPGYIGSR-NH2 (Lam.B1-(925-933)), and is immunologically similar to a previously described 67-kDa **laminin** receptor. In whole cell receptor assays, mEGF-(33-42), Lam. B1-(925-933), and **laminin** all have IC50 values for displacement of 125I-**laminin** in the range 1-5 nM. Cell attachment to solid-phase **laminin** is also blocked by all three ligands, but in contrast to the receptor assays, mEGF-(33-42) or Lam.B1-(925-933), while equipotent with each other, were less effective than **laminin**. The concentrations of the peptides required to produce half-maximal inhibition of attachment were in the range 230-390 nM, but those for **laminin** were 1000-fold lower, in the range 0.2-0.3 nM. Like **laminin**, solid-phase mEGF-(33-42) supports cell attachment, and this ability is blocked by anti-67-kDa receptor antibodies. Modeling studies suggest that both peptides present a tyrosyl and an arginyl residue on the same face of a right-handed helical fold with elliptical cross-section.

L29 ANSWER 14 OF 35 MEDLINE

ACCESSION NUMBER: 96200331 MEDLINE
DOCUMENT NUMBER: 96200331 PubMed ID: 8625323

TITLE: Urokinase receptor antagonists inhibit angiogenesis and primary tumor growth in syngeneic mice.

AUTHOR: Min H Y; Doyle L V; Vitt C R; Zandonella C L; Stratton-Thomas J R; Shuman M A; Rosenberg S

CORPORATE SOURCE: Chiron Corporation, Emeryville, California 94608, USA.

SOURCE: CANCER RESEARCH, (1996 May 15) 56 (10) 2428-33.
Journal code: 2984705R. ISSN: 0008-5472.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199606
ENTRY DATE: Entered STN: 19960708
Last Updated on STN: 20000303
Entered Medline: 19960626

AB Urokinase plasminogen activator (uPA) and its receptor are key components of a cell surface proteolytic cascade used by tumor cells and capillary endothelial cells for basement membrane invasion, a process required for

metastasis and angiogenesis. We have cloned, expressed, and purified the **epidermal growth factor**-like domain of **murine** uPA alone and fused it to the Fc portion of human IgG as high-affinity murine urokinase receptor antagonists. These molecules are potent inhibitors of murine urokinase binding to its receptor and inhibit angiogenesis in an in vitro model of capillary tube formation in fibrin gels. In vivo, basic fibroblast growth factor-induced neovascularization and B16 melanoma growth in syngeneic mice are also substantially suppressed by these molecules. Coupled with previous studies showing inhibition of metastasis, these findings suggest that urokinase receptor antagonists may be useful therapeutically as inhibitors of tumor progression.

L29 ANSWER 15 OF 35 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 96196434 MEDLINE
DOCUMENT NUMBER: 96196434 PubMed ID: 8648630
TITLE: Crystal structure of three consecutive **laminin** -type epidermal growth factor-like (LE) modules of **laminin** gammal chain harboring the nidogen binding site.
AUTHOR: Stetefeld J; Mayer U; Timpl R; Huber R
CORPORATE SOURCE: Abteilungen fur Strukturforschung and Proteinchemie, Max-Planck-Institut fur Biochemie, Martinsried, Germany.
SOURCE: JOURNAL OF MOLECULAR BIOLOGY, (1996 Apr 5) 257 (3) 644-57. Journal code: 2985088R. ISSN: 0022-2836.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199607
ENTRY DATE: Entered STN: 19960805
Last Updated on STN: 20000303
Entered Medline: 19960722

AB The structure of three consecutive **laminin**-type **EGF** -like (LE) modules of **mouse laminin** gammma1 chain, gamma1III3-5 (positions 738 to 899), has been determined by multiple isomorphous replacement in a crystal of space group p6(4)22 (a=b=74.57 angstroms, c = 185.11 angstroms and gamma = 120 degrees). The crystal structure was refined using restrained crystallographic refinement to an R-factor of 19.72% for 14,983 independent reflections with intensities F(obs)> 0 at 2.1 angstroms resolution, with root mean square deviation of 0.012 angstroms and 1.690 degrees from ideal bond lengths and bond angles, respectively. The final model consisted of 1179 (non-hydrogen) protein atoms within 162 residues and 119 water molecules. The molecule showed a rod-like structure of about 76 angstroms length with individual modules twisted relative to each other by about 70 degrees. Each module has the same disulfide bond connections Cys1-Cys3 (loop a), Cys2-Cys4 (loop b), Cys5-Cys6 (loop c) and Cys7-Cys8 (loop d), the first three being identical to epidermal growth factor (EGF). All three LE modules showed little secondary structure which was mainly restricted to loop d, but they differed in several other details of their structure. The interface contacts between the LE modules are based on hydrogen bonds and hydrophobic interactions between the hydrophobic core of loop d of the preceding module and the first cysteine and an exposed residue in loop b of the following module. Module 4 was previously shown to contribute the major nidogen binding site of laminis and site-directed mutagenesis demonstrated a specific binding role for Asp800, Asn802, Val804 and Tyr819 in loops a and c. The side-chain of these four residues are all located on the surface in a linear array and separated by a distance of 17

angstroms between Tyr819 and Val804. The entire nidogen binding site is stabilized via main-chain hydrogen bonds which are in part derived from the link between loops b and c (residues Leu815 and Lys816). The data demonstrate the unique nature of the LE modules and only a remote similarity to EGF. They also indicate that the crucial residues in the binding loops provide direct contacts with nidogen and explain the synergism between loops a and c which is essential for binding.

L29 ANSWER 16 OF 35 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:14779 HCAPLUS
DOCUMENT NUMBER: 124:46579
TITLE: Production and characterization of WEG-1, an epidermal growth factor/transforming growth factor-.alpha.-responsive mouse uterine epithelial cell line
AUTHOR(S): Wegner, Carole C.; Cherington, Van; Clemens, Jeffrey W.; Jacobs, Andrew L.; Julian, Joanne; Surveyor, Gulnar A.; Bell, Ewen C.; Carson, Daniel D.
CORPORATE SOURCE: Dep. Biochemistry and Molecular Biology, M.D. Anderson Cancer Center, Houston, TX, 77030, USA
SOURCE: Endocrinology (1996), 137(1), 175-84
CODEN: ENDOAO; ISSN: 0013-7227
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Uterine epithelial cells (UEC) isolated from 6-wk-old CF-1 mice were immortalized using retroviral-mediated transfection of SV40 large T-antigen. One line, WEG-1, retained epithelial morphol. and reacted with antibodies to cytokeratins 18, 19, **laminin**, fibronectin, and .beta.-catenin. In addn., WEG-1 cells displayed strong nuclear immunoreactivity to SV40 large T-antigen, confirming integration of the retrovirus vector and expression of this gene. WEG-1 cells were neg. for nonepithelial markers such as desmin and factor 8. WEG-1 cells did not proliferate in serum-free medium; however, addn. of 0.5% FBS supported proliferation to the same extent as 10% FBS. Addn. of 50 ng/mL EGF to medium contg. 0.5% charcoal-stripped FBS restored proliferation comparable with 0.5% whole FBS. EGF or transforming growth factor-.alpha. (50 ng/mL), but not transforming growth factor-.beta., leukemia-inhibiting factor, or FGF, induced the secretion of three proteins (Mr .simeq. 158K, 148K, and 36K). Comparison of protein secretions of WEG-1 cells and UEC showed shared as well as distinct bands. Like UEC, WEG-1 cells secreted PGF2.alpha. and PGE2 and expressed PGH synthase-2. Unlike UEC, WEG-1 cells showed no apical/basal preference for either uptake for methionine or secretion of proteins. The absence of immunoreactive E-cadherin or zona occludens-1 was consistent with the absence of cell polarity in WEG-1 cells. Primary UEC, which polarize in vitro, do not support blastocyst attachment. WEG-1 cells, although not polarized in vitro, also exhibited delayed blastocyst attachment compared with nonuterine cell lines, suggesting that WEG-1 cells partially retained some aspects of UEC function relevant to embryo attachment. WEG-1 cells expressed mRNA for Muc-1, an UEC mucin suggested to have antiadhesive properties. Furthermore, WEG-1 cells did not display high-affinity heparin binding sites, an activity assocd. with embryo attachment. WEG-1 cells may provide a model for studying various aspects of UEC function and murine embryo attachment.

L29 ANSWER 17 OF 35 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:120727 HCAPLUS
DOCUMENT NUMBER: 124:221553
TITLE: A peptide molecular dynamics study correlates

structure with function
AUTHOR(S): **McFerran, Neil V.; Walker, Brian; Nelson, John**
CORPORATE SOURCE: Division of Biochemistry, Queen's Univ. of Belfast, Belfast, BT9 7BL, UK
SOURCE: Biochemical Society Transactions (1996), 24(1), 127S
CODEN: BCSTB5; ISSN: 0300-5127
PUBLISHER: Portland Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Peptide mol. dynamics was used to study the conformation of the amino acid residue 33-42 (CVIGYSGDRC) of **murine epidermal growth factor** (**EGF**) C-loop and the EGF-like domain (CDPGYIGSR) from **laminin** B1 chain. Both peptides adopted a very similar open right handed helical fold. Their similarity in conformation might play a role in their receptor binding activities.

L29 ANSWER 18 OF 35 MEDLINE
ACCESSION NUMBER: 95395967 MEDLINE
DOCUMENT NUMBER: 95395967 PubMed ID: 7666532
TITLE: Retroviral retargeting by envelopes expressing an N-terminal **binding** domain.
AUTHOR: Cosset F L; Morling F J; Takeuchi Y; Weiss R A; Collins M K; Russell S J
CORPORATE SOURCE: Institute of Cancer Research: Chester Beatty Laboratories, London, United Kingdom.
SOURCE: JOURNAL OF VIROLOGY, (1995 Oct) 69 (10) 6314-22.
Journal code: 0113724. ISSN: 0022-538X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199510
ENTRY DATE: Entered STN: 19951020
Last Updated on STN: 20020924
Entered Medline: 19951012
AB We have engineered ecotropic Moloney murine leukemia virus-derived envelopes targeted to cell surface molecules expressed on human cells by the N-terminal insertion of polypeptides able to **bind** either Ram-1 phosphate transporter (the first 208 amino acids of amphotropic **murine** leukemia virus surface protein) or **epidermal growth factor** receptor (EGFR) (the 53 amino acids of EGF). Both envelopes were correctly processed and incorporated into viral particles. Virions carrying these envelopes could specifically **bind** the new cell surface receptors. Virions targeted to Ram-1 could infect human cells, although the efficiency was reduced compared with that of virions carrying wild-type amphotropic murine leukemia virus envelopes. The infectivity of virions targeted to EGFR was **blocked** at a postbinding step, and our results suggest that EGFR-bound virions were rapidly trafficked to lysosomes. These data suggest that retroviruses require specific properties of cell surface molecules to allow the release of viral cores into the correct cell compartment.

L29 ANSWER 19 OF 35 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 95368631 MEDLINE
DOCUMENT NUMBER: 95368631 PubMed ID: 7543818
TITLE: **Murine epidermal growth factor** (**EGF**) fragment (33-42) inhibits

Search completed by David Schreiber 308-4292

both EGF- and **laminin**-dependent endothelial cell motility and angiogenesis.

AUTHOR: **Nelson J**; Allen W E; Scott W N; Bailie J R; **Walker B**; **McFerran N V**; Wilson D J

CORPORATE SOURCE: Division of Biochemistry, School of Biology and Biochemistry, Queen's University of Belfast, Northern Ireland, United Kingdom.

SOURCE: CANCER RESEARCH, (1995 Sep 1) 55 (17) 3772-6.
Journal code: 2984705R. ISSN: 0008-5472.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199509
ENTRY DATE: Entered STN: 19950930
Last Updated on STN: 20000303
Entered Medline: 19950918

AB **Laminin**, **murine epidermal growth factor** (mEGF), and the synthetic **laminin** peptide Lam.B1(925-933) (a linear peptide from the B1 chain of murine **laminin**, CDPGY1GSR-amide) all stimulate endothelial cell motility above basal rates, whereas a synthetic mEGF fragment, mEGF33-42 (a linear peptide from the C-loop of mEGF, acetyl-C-[S-Acm]-VIGYSGDR-C-[S-Acm]-amide), inhibits motility. In both human SK HEP-1 and embryonic chick endothelial cells, mEGF33-42 blocks both EGF- and **laminin** -stimulated locomotion of endothelial cells. In vivo, mEGF33-42 also blocks both **laminin**- and mEGF-induced angiogenesis in the chick. In the human cell line. Lam.B1(925-933) has an additive effect in coincubation with either **laminin** or mEGF, but it blocks their effects in the chick cells. Lam.B1(925-933) alone stimulates angiogenesis in the chick but blocks **laminin**-induced angiogenesis. Thus, mEGF33-42 acts as a general **laminin** antagonist, whereas Lam.B1(925-933) acts as a **laminin** agonist in human cells, but in chick cells it acts as a partial antagonist. We propose that the presence of an anionic group at the eighth residue of mEGF33-42 may be the source of the antagonistic effects seen with this peptide as compared with the **laminin** fragment. These findings have important implications in the design of human antiangiogenic agents, and also in the use of chick models in the study of human disease.

L29 ANSWER 20 OF 35 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1994:648874 HCAPLUS
DOCUMENT NUMBER: 121:248874

TITLE: Two non-contiguous regions contribute to nidogen binding to a single EGF-like motif of the **laminin** .gamma.1 chain

AUTHOR(S): Poeschl, Ernst; Fox, Jay W.; Block, Dirk; Mayer, Ulrike; Timpl, Rupert

CORPORATE SOURCE: Max-Planck Connective Tissue Clinical Research Group for Rheumatology, Erlangen, D-91054, Germany

SOURCE: EMBO Journal (1994), 13(16), 3741-7
CODEN: EMJODG; ISSN: 0261-4189

DOCUMENT TYPE: Journal
LANGUAGE: English

AB High affinity binding of nidogen to **laminin** is mediated by an EGF-like repeat .gamma.1III4 of the mouse **laminin** .gamma.1 chain and has now been restricted to two short noncontiguous regions of its 56 residue sequence by use of synthetic peptides and recombinant mutants. Disulfide loop a,b of the repeat and a modified loop a,c could completely

inhibit binding, with a 5000-fold or 300-fold reduced affinity resp. Synthetic loops c and d lacked inhibitory activity. Some binding contribution of Tyr819 in loop c was, however, shown by mutation and side chain modification. Together with studies of loop chimeras, this indicated a distinct cooperativity between the two binding sites. The major binding site of loop a was localized to the heptapeptide NIDPNAV (position 798-804). A change of Asp800 to Asn or Ala803 to Val caused a strong redn. in binding activity, while only small effects were obsd. for the changes Pro801 to Gln and Ile799 to Val. The latter replacement corresponds to the single substitution found in the same region of the Drosophila **laminin** .gamma.1 chain. However, the changes Asn802 to Ser or Val804 to Ser, both known to exist in the **laminin** .gamma.2 chain, were deleterious mutations. This demonstrated conservation of binding structures in **laminins** of distantly related species, but not between homologous chains of **laminin** isoforms.

L29 ANSWER 21 OF 35 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 93349872 MEDLINE
DOCUMENT NUMBER: 93349872 PubMed ID: 8394119
TITLE: Preparation and characterization of a bifunctionally spin-labeled **mutant** of **murine epidermal growth factor** for saturation-transfer electron paramagnetic resonance studies of the growth factor/receptor complex.
AUTHOR: Rousseau D L Jr; Guyer C A; Beth A H; Papayannopoulos I A; Wang B; Wu R; Mroczkowski B; Staros J V
CORPORATE SOURCE: Department of Biochemistry, Vanderbilt University, Nashville, Tennessee 37235.
CONTRACT NUMBER: P01 CA43720 (NCI)
RR00317 (NCRR)
SOURCE: BIOCHEMISTRY, (1993 Aug 10) 32 (31) 7893-903.
Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199309
ENTRY DATE: Entered STN: 19931001
Last Updated on STN: 20000303
Entered Medline: 19930916

AB In this report we describe the production of a [Lys3,Tyr22] **murine epidermal growth factor** (mEGF) **mutant** for spin-labeling with bis(sulfo-N-succinimidyl)-[15N,2H16]doxyl-2-spiro-4'-pimelate ([15N,2H16]BSSDP) in order to study the rotational dynamics of the EGF/EGF receptor complex by saturation-transfer electron paramagnetic resonance (ST-EPR). Previous results [Faulkner-O'Brien et al. (1991) Biochemistry 30,8976-8985] indicated that the reaction of [15N,2H16]BSSDP with wild-type mEGF did not yield a product useful for ST-EPR studies of the EGF/EGF receptor complex because the major product, in which [15N,2H16]BSSDP was attached only at the amino terminus of mEGF, lacked rigid motional coupling of the spin probe to the protein, and the more tightly coupled bidentate product was unstable. Using oligonucleotide-mediated site-directed **mutagenesis** of a synthetic gene for mEGF, we **replaced** Tyr3 with Lys and His22 with Tyr in wild-type mEGF to produce a **mutant** mEGF suitable for [15N,2H16]BSSDP labeling. The [Lys3,Tyr22] mEGF was expressed in Escherichia coli HB101 transformed with a pIN-III-ompA3-[Lys3,Tyr22] mEGF plasmid and was purified from the bacterial periplasm using a simple two

step purification method. The [15N,2H16]BSSDP reacted with [Lys3,Tyr22]mEGF in high yield, and EPR analysis of the major product revealed tight motional coupling between the spin probe and the protein. Biological activity, as assessed by stimulation of EGF receptor autophosphorylation and dimerization, was not affected by either the **mutations** or the addition of the spin label. The [15N,2H16]BSSDP-**modified** [Lys3,Tyr22] mEGF was shown to be equipotent with mEGF in EGF receptor competition **binding** assays using A431 cells; in EPR studies, mEGF also was shown to specifically **block** [15N,2H16]BSSDP-**modified** [Lys3,Tyr22]mEGF **binding** to the EGF receptor in A431 membrane vesicles. Using the [15N,2H16]BSSDP-**modified** [Lys3,Tyr22]mEGF, we now report the first measurement of the rotational dynamics of the EGF/EGF receptor complex in A431 membrane vesicles by ST-EPR.

L29 ANSWER 22 OF 35 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:154749 HCAPLUS
DOCUMENT NUMBER: 120:154749
TITLE: Generation and characterization of a mouse fibroblast system for examining the effects of EGF on **laminin**-induced chemotaxis
AUTHOR(S): Lin, Meei Lih
CORPORATE SOURCE: Univ. Wisconsin, Madison, WI, USA
SOURCE: (1992) 165 pp. Avail.: Univ. Microfilms Int., Order No. DA9306468
From: Diss. Abstr. Int. B 1993, 54(4), 1757
DOCUMENT TYPE: Dissertation
LANGUAGE: English
AB Unavailable

L29 ANSWER 23 OF 35 SCISEARCH COPYRIGHT 2003 THOMSON ISI
ACCESSION NUMBER: 91:472750 SCISEARCH
THE GENUINE ARTICLE: GB517
TITLE: IDENTIFICATION OF 2 36-KD PHOSPHOPROTEINS ASSOCIATED WITH ALTERED DIFFERENTIATION IN RETROVIRUS-TRANSFORMED BALB/MK-2 MOUSE KERATINOCYTES
AUTHOR: MAKINO J K; WEISSMAN B E (Reprint)
CORPORATE SOURCE: UNIV N CAROLINA, DEPT PATHOL, CHAPEL HILL, NC, 27599 (Reprint); UNIV N CAROLINA, LINEBERGER CANC RES CTR, CHAPEL HILL, NC, 27599
COUNTRY OF AUTHOR: USA
SOURCE: PATHOBIOLOGY, (1991) Vol. 59, No. 6, pp. 384-390.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: ENGLISH
REFERENCE COUNT: 25
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Balb/MK-2 cells, derived from **mouse epidermal** keratinocytes, require **epidermal growth factor** (EGF) for growth and undergo terminal differentiation when exposed to extracellular calcium levels greater than 1.0 mM. Transformation of these cells by a variety of acute transforming viruses abrogates the EGF requirement and **blocks** terminal differentiation. In general, oncogenes coding for tyrosine kinase oncoproteins abolish differentiation at an earlier step than those of the ras gene family. We therefore examined whether alterations in protein phosphorylation occur during differentiation of the Balb/MK-2 cells and two different viral transformants. Only one 36-kD phosphoprotein emerged whose phosphorylation consistently changed during epidermal differentiation.

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Modifications in the phosphorylation of a second 36-kD protein occurred in the virally transformed cell lines. Phosphoamino acid analysis of the proteins demonstrated only the presence of phosphoserine residues. These studies define changes in protein phosphorylation associated with the regulation of epidermal differentiation.

L29 ANSWER 24 OF 35 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1992:65161 BIOSIS
DOCUMENT NUMBER: BR42:29061
TITLE: CELLULAR MODEL FOR EXAMINING EGF **LAMININ** INTERACTIONS GENERATION OF **LAMININ**-BINDING CELL LINES FROM AN EGF RECEPTOR POSITIVE CELL LINE CONTAINING NO **LAMININ** BINDING ACTIVITY.
AUTHOR(S): LIN M-L; BERTICS P J
CORPORATE SOURCE: DEP. PHYSIOL. CHEM., UNIV. WIS., MADISON, WIS. 53706.
SOURCE: ABSTRACTS OF PAPERS PRESENTED AT THE THIRTY-FIRST ANNUAL MEETING OF THE AMERICAN SOCIETY FOR CELL BIOLOGY, BOSTON, MASSACHUSETTS, USA, DECEMBER 8-12, 1991. J CELL BIOL, (1991) 115 (3 PART 2), 113A.
CODEN: JCLBA3. ISSN: 0021-9525.
DOCUMENT TYPE: Conference
FILE SEGMENT: BR; OLD
LANGUAGE: English

L29 ANSWER 25 OF 35 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 91104979 MEDLINE
DOCUMENT NUMBER: 91104979 PubMed ID: 2271672
TITLE: Resistance to receptor-mediated degradation of a **murine epidermal growth factor** analogue (**EGF**-Val-47) potentiates its mitogenic activity.
AUTHOR: Walker F; Nice E; Fabri L; Moy F J; Liu J F; Wu R; Scheraga H A; Burgess A W
CORPORATE SOURCE: Melbourne Branch, Ludwig Institute for Cancer Research, Victoria, Australia.
SOURCE: BIOCHEMISTRY, (1990 Nov 27) 29 (47) 10635-40.
Journal code: 0370623. ISSN: 0006-2960.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199102
ENTRY DATE: Entered STN: 19910329
Last Updated on STN: 20000303
Entered Medline: 19910228

AB In most cell types two classes of epidermal growth factor (EGF) receptors can be found: a major class that binds EGF with relatively low affinity and a minor class that binds with very high affinity. Structure-function studies have shown that mutations at amino acid 47 in the EGF molecule severely reduce its affinity for the EGF receptor but do not cause preferential binding to one or the other subclass of receptors. Using three EGF derivatives with a mutation at amino acid 47 (Ser-47, Leu-37-Tyr-47, and Val-47), we have investigated the relative contribution of the two receptor subclasses to the EGF-dependent mitogenic response. We show that mitogenicity correlates exclusively with occupancy of the high-affinity receptor and that full occupancy of this subclass is required for maximal stimulation. In addition we demonstrate that for the EGF-Val-47 analogue this requirement can be abrogated and half-maximal biological activity reached with a high-affinity receptor occupancy of

only 8%. While the rate of internalization did not significantly differ between EGF-Val-47 and native mEGF, the analogue was much more **resistant** to degradation by cellular **proteases** and, after binding and receptor-mediated internalization, was released into the medium predominantly in an intact form. We propose that the increased mitogenicity of EGF-Val-47 is due to its prolonged half-life, resulting in continued occupancy of the high-affinity EGF receptor.

L29 ANSWER 26 OF 35 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 90384794 MEDLINE
DOCUMENT NUMBER: 90384794 PubMed ID: 2119494
TITLE: Transcription factor PEA3 participates in the induction of urokinase plasminogen activator transcription in **murine** keratinocytes stimulated with **epidermal growth factor** or phorbol-ester.
AUTHOR: Rorth P; Nerlov C; Blasi F; Johnsen M
CORPORATE SOURCE: Institute of Microbiology, University of Copenhagen, Denmark.
SOURCE: NUCLEIC ACIDS RESEARCH, (1990 Sep 11) 18 (17) 5009-17. Journal code: 0411011. ISSN: 0305-1048.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-X52971
ENTRY MONTH: 199010
ENTRY DATE: Entered STN: 19901122
Last Updated on STN: 20000303
Entered Medline: 19901024

AB Keratinocytes in culture represent cells which exhibit continued and controlled growth in the organism. We have investigated the synthesis of urokinase plasminogen activator mRNA in exponentially growing cultures of primary murine keratinocytes and the keratinocyte cell line BALB/MK. The tumor promotor 12-O-tetradecanoyl phorbol-13-acetate (TPA) and epidermal growth factor (EGF) induced urokinase mRNA synthesis. We made a series of progressive 5' deletions as well as internal deletions in the region upstream of the murine uPA gene. These were joined to the cat reporter gene, and used to map the TPA and EGF responsive regions of the promoter. We found both responsive sequences within a 90 base pair Hae III fragment, located 2.4 kb. upstream of the mRNA **cap** site. This DNA fragment conferred TPA inducibility on reporter gene expression independent of its distance and orientation to the transcription initiation site. Footprinting and gel retardation studies identified the responsible sequence to be a **binding** site for PEA3 juxtaposed to an octameric TRE-element. Transfections with point **mutants** showed that these target sequences were necessary for TPA and EGF induction of transcription.

L29 ANSWER 27 OF 35 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1990:161955 BIOSIS
TITLE: STRUCTURE AND FUNCTION OF **LAMININ** ANATOMY OF A MULTIDOMAIN GLYCOPROTEIN.
AUTHOR(S): BECK K; HUNTER I; ENGEL J
CORPORATE SOURCE: INST. BIOPHYS., UNIV., A-4040 LINZ, AUSTRIA.
SOURCE: FASEB J., (1990) 4 (2), 148-160. CODEN: FAJOEC. ISSN: 0892-6638.
FILE SEGMENT: BR; OLD
LANGUAGE: English

Search completed by David Schreiber 308-4292

L29 ANSWER 28 OF 35 MEDLINE DUPLICATE 11
ACCESSION NUMBER: 88302137 MEDLINE
DOCUMENT NUMBER: 88302137 PubMed ID: 3136317
TITLE: Release of a phorbol ester-induced mitogenic **block** by **mutation** at Thr-654 of the epidermal growth factor receptor.
AUTHOR: Livneh E; Dull T J; Berent E; Prywes R; Ullrich A; Schlessinger J
CORPORATE SOURCE: Department of Chemical Immunology, Weizmann Institute of Science, Rehovot, Israel.
CONTRACT NUMBER: CA-25820 (NCI)
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (1988 Jun) 8 (6) 2302-8. Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198809
ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 20000303
Entered Medline: 19880916

AB The tumor promoter phorbol ester (TPA) modulates the **binding** affinity and the mitogenic capacity of the epidermal growth factor (EGF) receptor. Moreover, TPA-induced kinase C phosphorylation occurs mainly on Thr-654 of the EGF receptor, suggesting that the phosphorylation state of this residue regulates ligand-**binding** affinity and kinase activity of the EGF receptor. To examine the role of this residue, we prepared a Tyr-654 EGF receptor cDNA construct by in vitro site-directed **mutagenesis**. Like the wild-type receptor, the **mutant** receptor exhibited typical high- and low-affinity **binding** sites when expressed on the surface of NIH 3T3 cells. Moreover, TPA regulated the affinity of both wild-type and **mutant** receptors and stimulated receptor phosphorylation of serine and threonine residues other than Thr-654. The addition of TPA to NIH 3T3 cells expressing a wild-type human EGF receptor **blocked** the mitogenic capacity of EGF. However, this inhibition did not occur in cells expressing the Tyr-654 EGF receptor **mutant**. In the latter cells, EGF was able to stimulate DNA synthesis even in the presence of inhibitory concentrations of TPA. While phosphorylation of sites other than Thr-654 may regulate ligand-**binding** affinity, the phosphorylation of Thr-654 by kinase C appears to provide a negative control mechanism for **EGF**-induced mitogenesis in **mouse** NIH 3T3 fibroblasts.

L29 ANSWER 29 OF 35 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1988:369842 BIOSIS
DOCUMENT NUMBER: BR35:54455
TITLE: GROWTH FACTOR LIKE DOMAINS IN **LAMININ**.
AUTHOR(S): END P; ENGEL J; PANAYOTOU G; TIMPL R
CORPORATE SOURCE: MRC, LONDON.
SOURCE: SYMPOSIUM ON GROWTH FACTORS AND THEIR RECEPTORS: GENETIC CONTROL AND RATIONAL APPLICATION HELD AT THE 17TH ANNUAL MEETING OF THE UCLA (UNIVERSITY OF CALIFORNIA-LOS ANGELES) SYMPOSIA ON MOLECULAR AND CELLULAR BIOLOGY, KEYSTONE, COLORADO, USA, JANUARY 24-30, 1988. J CELL BIOCHEM SUPPL, (1988) 0 (12 PART A), 81.
CODEN: JCBSD7.
DOCUMENT TYPE: Conference
FILE SEGMENT: BR; OLD

Search completed by David Schreiber 308-4292

LANGUAGE: English

L29 ANSWER 30 OF 35 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1987:206611 BIOSIS
DOCUMENT NUMBER: BA83:104241
TITLE: SEQUENCE OF THE COMPLEMENTARY DNA ENCODING THE **LAMININ** B1 CHAIN REVEALS A MULTIDOMAIN PROTEIN CONTAINING CYSTEINE-RICH REPEATS.
AUTHOR(S): SASAKI M; KATO S; KOHNO K; MARTIN G R; YAMADA Y
CORPORATE SOURCE: LAB. DEV. BIOL. ANOMALIES, NATL. INST. DENTAL RES., NATL. INST. HEALTH, BETHESDA, MD. 20892.
SOURCE: PROC NATL ACAD SCI U S A, (1987) 84 (4), 935-939. CODEN: PNASA6. ISSN: 0027-8424.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB **Laminin** is a basement membrane-specific glycoprotein (800 kDa) consisting of three chains: A, B1, and B2. **Laminin** has diverse biological functions, which include stimulating epithelial cell growth and differentiation. We have isolated two overlapping cDNA clones that span 5.9 kilobases and code for the entire B1 chain of mouse **laminin.** The nucleotide sequence of the clones reveals a 5358-base pair open reading frame that potentially codes for 1786 amino acids, including 20 amino acids of a presumptive signal peptide. Analysis of the deduced protein sequence predicts that the B1 chain has seven distinct domains that include cysteine-rich repeats, .alpha.-helical, and globular structures. Part of the cysteine-rich region is homologous to epidermal growth factor and other proteins that contain epidermal growth factor-like repeats.

L29 ANSWER 31 OF 35 MEDLINE DUPLICATE 12
ACCESSION NUMBER: 87166210 MEDLINE
DOCUMENT NUMBER: 87166210 PubMed ID: 3494020
TITLE: Loss of growth responsiveness to epidermal growth factor and enhanced production of alpha-transforming growth factors in ras-transformed mouse mammary epithelial cells.
AUTHOR: Salomon D S; Perroteau I; Kidwell W R; Tam J; Derynck R
CONTRACT NUMBER: CA 36544 (NCI)
SOURCE: JOURNAL OF CELLULAR PHYSIOLOGY, (1987 Mar) 130 (3) 397-409. Journal code: 0050222. ISSN: 0021-9541.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198705
ENTRY DATE: Entered STN: 19900303
Last Updated on STN: 20000303
Entered Medline: 19870508
AB A mouse mammary epithelial cell line, NMuMG, exhibits a low capacity to grow in semisolid medium as colonies and it is not tumorigenic in nude mice. In contrast, NMuMG cells which have been transformed by an activated c-Harvey ras proto-oncogene, NMuMG/rasH, or by the polyoma middle T-transforming gene, NMuMG/pyt, are able to grow in soft agar and, when injected into nude mice, produce undifferentiated carcinomas. Human epidermal growth factor (EGF) or human alpha-transforming growth factor (alpha TGF) can stimulate, in a dose-dependent fashion, the anchorage-independent growth of NMuMG and NMuMG/pyt cells in soft agar but fail to enhance the anchorage-independent growth of the NMuMGrasH cells. Likewise, human EGF or human alpha TGF is also able to stimulate the anchorage-dependent growth of normal NMuMG cells and NMuMG/pyt cells in a

serum-free medium supplemented with insulin, transferrin, fetuin, and **laminin**, or in medium containing low concentrations of serum, whereas these same growth factors under comparable culture conditions have little or no effect upon the anchorage-dependent growth of the ras-transformed NMuMG-rasH cells. The biological refractoriness of the NMuMG/rasH cells to human EGF or human alpha TGF is reflected by a reduction in the total number of cell surface receptors for EGF and by an absence of a high-affinity population of binding sites for **mouse** [125I]**EGF** on these cells as compared to the NMuMG or NMuMG/pyt cells. In addition, concentrated conditioned medium (CM) obtained from NMuMG/rasH and NMuMG/pyt cells contains a relatively higher amount of biologically active TGFs than CM obtained from comparably treated NMuMG cells as measured by the ability to induce the anchorage-independent growth of normal rat kidney cells in soft agar. The higher levels of biologically active TGFs found in the CM from the transformed cells relative to the NMuMG cells is paralleled by a corresponding increase in the CM from these cells in the amount of immunoreactive alpha TGF, by an increase in the amount of EGF receptor-competing activity, and by an increase in the levels of alpha TGF mRNA in the NMuMG/rasH cells. These results demonstrate that mammary epithelial cells which have been transformed by an activated ras proto-oncogene, but not by the polyoma middle T-transforming gene, become unresponsive to exogenous EGF or alpha TGF.(ABSTRACT TRUNCATED AT 400 WORDS)

L29 ANSWER 32 OF 35 MEDLINE DUPLICATE 13
ACCESSION NUMBER: 87134684 MEDLINE
DOCUMENT NUMBER: 87134684 PubMed ID: 3493183
TITLE: Localization and quantitation of 125I-**epidermal growth factor binding** in **mouse** embryonic tooth and other embryonic tissues at different developmental stages.
AUTHOR: Partanen A M; Thesleff I
SOURCE: DEVELOPMENTAL BIOLOGY, (1987 Mar) 120 (1) 186-97. Journal code: 0372762. ISSN: 0012-1606.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198704
ENTRY DATE: Entered STN: 19900303
Last Updated on STN: 20000303
Entered Medline: 19870406

AB We have shown earlier that epidermal growth factor (EGF) inhibits morphogenesis and cell differentiation in mouse embryonic teeth in organ culture. This inhibition depends on the stage of tooth development so that only teeth at early developmental stages respond to EGF (A-M. Partanen, P. Ekblom, and I. Thesleff (1985) Dev. Biol. 111, 84-94). We have now studied the quantity and pattern of EGF **binding** in teeth at various stages of development by incubating the dissected tooth germs with 125I-labeled EGF. Although the quantity of 125I-EGF **binding** per microgram DNA stays at the same level, localization of 125I-EGF **binding** by autoradiography reveals that the distribution of **binding** sites changes dramatically. In bud stage the epithelial tooth bud that is intruding into the underlying mesenchyme has **binding** sites for EGF, but the condensation of dental mesenchymal cells around the bud does not **bind** EGF. At the **cap** stage of development the dental mesenchyme **binds** EGF, but the dental epithelium shows no **binding**. This indicates that the dental mesenchyme is the primary target tissue for the inhibitory

effect of EGF on tooth morphogenesis during early **cap** stage. During advanced morphogenesis the **binding** sites of EGF disappear also from the dental papilla mesenchyme, but the dental follicle which consists of condensed mesenchymal cells surrounding the tooth germ, **binds** EGF abundantly. We have also studied EGF **binding** during the development of other embryonic organs, kidney, salivary gland, lung, and skin, which are all formed by mesenchymal and epithelial components. The patterns of EGF **binding** in various tissues suggest that EGF may have a role in the organogenesis of epitheliomesenchymal organs as a stimulator of epithelial proliferation during initial epithelial bud formation and branching morphogenesis. The results of this study indicate that EGF stimulates or maintains proliferation of undifferentiated cells during embryonic development and that the expression of EGF receptors in different organs is not related to the age of the embryo, but is specific to the developmental stage of each organ.

L29 ANSWER 33 OF 35 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1984:195844 BIOSIS
DOCUMENT NUMBER: BA77:28828
TITLE: A NEW DIFFERENTIATED CELL LINE DIF-5 DERIVED BY RETINOIC-ACID TREATMENT OF F-9 TERATO CARCINOMA CELLS CAPABLE OF EXTRACELLULAR MATRIX PRODUCTION AND GROWTH IN THE ABSENCE OF SERUM.
AUTHOR(S): NAGARAJAN L; JETTEN A M; ANDERSON W B
CORPORATE SOURCE: LAB. TUMOR IMMUNOLOGY AND BIOL., NATL. CANCER INST., BUILD. 10, RM. B1B 38 BETHESDA, MD 20205.
SOURCE: EXP CELL RES, (1983) 147 (2), 315-328.
CODEN: ECREAL. ISSN: 0014-4827.
FILE SEGMENT: BA; OLD
LANGUAGE: English

AB Treatment of F9 mouse teratocarcinoma cells with all trans retinoic acid (RA) causes them to differentiate into 2 or 3 morphologically distinct cell types. Whereas the majority of these retinoid-derived cells exhibit properties resembling parietal endoderm, a small percentage of this differentiated cell population manifests properties distinct from the parietal endoderm cell type. The isolation and partial characterization of such a non-parietal endoderm cell line (Dif 5) derived from F9 cells following prolonged (44 days) exposure to 1 .mu.M retinoic acid are described. Unlike the retinoid-induced parietal endoderm-like cell population, which exhibits a dramatic, characteristic morphological change upon treatment with 8-bromo-cAMP, Dif 5 cells do not show any morphological change with exposure to this cAMP analog. Dif 5 cells synthesize and deposit an extracellular matrix consisting of several components of Reichert's membrane (fibronectin, **laminin** and type IV collagen). This new cell line does not synthesize .alpha.-fetoprotein but does secrete plasminogen activator. An interesting property of these cells is their ability to grow in the absence of serum or other hormonal supplements. Yet the Dif 5 cells do exhibit density-dependent inhibition of growth. Unlike the parent F9 cells or parietal yolk sac (PYS-2) cells, these cells do possess specific cell surface receptors for epidermal growth factor (EGF). The growth-arrested Dif 5 cells can be reinitiated to proliferate by the addition of fetal calf serum (FCS) or EGF. The properties of Dif 5 cells determined fail to fulfill all the characteristics described for either parietal or visceral endodermal cells. This raises the possibility that Dif 5 cells might represent an endodermal cell type which is intermediate in differentiation to either parietal of visceral endoderm but which lacks the biochemical signal to complete this stage of differentiation. This new Dif 5 cell line should be

of considerable value in studying the modulation of growth requirements and extracellular matrix formation during early embryonic development.

L29 ANSWER 34 OF 35 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1983:282336 BIOSIS
DOCUMENT NUMBER: BA76:39828
TITLE: RATES OF SYNTHESIS OF BASEMENT MEMBRANE PROTEINS BY DIFFERENTIATING TERATO CARCINOMA STEM CELLS AND THEIR MODULATION BY HORMONES.
AUTHOR(S): PREHM P; DESSAU W; TIMPL R
CORPORATE SOURCE: MAX-PLANCK-INST. BIOCHEMIE, D-8033 MARTINSRIED, MUNICH, WEST GER.
SOURCE: CONNECT TISSUE RES, (1982) 10 (3-4), 275-286.
CODEN: CVTRBC. ISSN: 0300-8207.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB The embryonal carcinoma mouse cell line F-9 was used as a convenient model for a quantitative study of the production of the basement proteins **laminin** and type IV collagen. Both proteins could be identified in the culture medium and cell layer by radioimmunoassays, metabolic labeling and immunofluorescence. More than 95% of the material is secreted into the medium. Lack of ascorbic acid inhibits secretion of type IV collagen but not of **laminin**. Induction of differentiation into endoderm-like cells by retinoic acid consistently caused, after a lag period of 2-3 days, a 5- to 10-fold increase in the production of basement membrane proteins but not of total protein. Dibutyryl cAMP further potentiated this specific effect particularly with respect to type IV collagen synthesis. Insulin, epidermal growth factor and nerve growth factor produced only moderate increases (10-60%) in the amount of **laminin** and type IV collagen. Effects of these hormones were only observed with certain doses and were quite variable between different experiments.

L29 ANSWER 35 OF 35 HCAPLUS COPYRIGHT 2003 ACS DUPLICATE 14
ACCESSION NUMBER: 1978:453738 HCAPLUS
DOCUMENT NUMBER: 89:53738
TITLE: Epidermal growth factor. Relationship between receptor regulation and mitogenesis in 3T3 cells
AUTHOR(S): Aharonov, Aharon; Pruss, Rebecca M.; Herschman, Harvey R.
CORPORATE SOURCE: Dep. Biol. Chem., Univ. California Sch. Med., Los Angeles, CA, USA
SOURCE: Journal of Biological Chemistry (1978), 253(11), 3970-7
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Exposure of confluent nondividing 3T3 cells to 10nM **mouse epidermal growth factor** (**EGF**) [62229-50-9] at 37.degree., followed by incubation for 4.5 h at 37.degree., decreasedthe **binding** capacity for EGF-125I by 70-85%. Scatchard anal. of the **binding** data indicated that the decrease of EGF-125I **binding** was due to a decrease in the no. of available EGF receptors/cell, without any change in the affinity of the receptors for EGF. This modulation of the EGF-receptor by the growth factor, termed down regulation, was dependent on temp., EGF concn., time, and the physiol. state of the cell. Receptor loss occurred at physiol. EGF concns. (0.1-10nM) which span the concn. range which is mitogenic for 3T3 cells. Maximal stimulation of either thymidine-3H uptake or cell division occurred at 1nM EGF, a concn. at which only 20% of the

EGF-receptor sites were occupied and down regulation was only 55% complete. Low EGF concns. (.ltoreq.1nM) resulted in down regulation of unoccupied EGF receptors. Down regulation of the EGF receptor also occurred in SV40-transformed 3T3 cells. Growing 3T3 cells exposed to EGF also lost available EGF receptors. In contrast to confluent cells, dividing 3T3 cells rapidly **replaced** EGF receptors on the surface of the cell, in the presence of EGF. When EGF was removed from the medium, the EGF receptor was quickly replenished; by 13 h 50% of the down regulated receptors were restored. All EGF **binding** capacity returned by 20 h after removal of the growth factor. The half-life of the EGF receptor, estd. by **blocking** protein synthesis with cycloheximide, was .apprx.6 h. The mitogenic response of the cells to EGF required the continuous presence of EGF over a 3-4-day period; in contrast, down regulation was completed within 4 h. Continued occupancy of a portion of the remaining and restored EGF surface receptors was essential for mitogenesis. The major role of the redn. of EGF receptors by receptor down regulation may be to adjust the cell's subsequent sensitivity to EGF.